SPECIAL ARTICLE

Addressing Parents' Concerns: Do Vaccines Cause Allergic or Autoimmune Diseases?

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ABSTRACT. Anecdotal case reports and uncontrolled observational studies in the medical literature claim that vaccines cause chronic diseases such as asthma, multiple sclerosis, chronic arthritis, and diabetes. Several biological mechanisms have been proposed to explain how vaccines might cause allergic or autoimmune diseases. For example, allergic diseases might be caused by prevention of early childhood infections (the "hygiene hypothesis"), causing a prolongation of immunoglobulin E-promoting T-helper cell type 2-type responses. However, vaccines do not prevent most common childhood infections, and large well-controlled epidemiologic studies do not support the hypothesis that vaccines cause allergies. Autoimmune diseases might occur after immunization because proteins on microbial pathogens are similar to human proteins ("molecular mimicry") and could induce immune responses that damage human cells. However, wild-type viruses and bacteria are much better adapted to growth in humans than vaccines and much more likely to stimulate potentially damaging self-reactive lymphocytes. Consistent with critical differences between natural infection and immunization, well-controlled epidemiologic studies do not support the hypothesis that vaccines cause autoimmunity.

Flaws in proposed biological mechanisms that explain how vaccines might cause chronic diseases are consistent with the findings of many well-controlled large epidemiologic studies that fail to show a causal relationship. ***Pediatrics*** **2003;111:653–659;** ***vaccines, vaccine safety, asthma, allergies, multiple sclerosis, diabetes, chronic arthritis.***

ABBREVIATIONS. IgE, immunoglobulin E; Th2, T-helper cell type 2; Th1, T-helper cell type 1; HMO, health maintenance organization; Hib, *Haemophilus influenzae* type b; MBP, myelin basic protein; HBsAg, hepatitis B surface antigen; OspA, outer surface protein A; LFA-1, lymphocyte function-associated antigen-1.

Anecdotal reports and uncontrolled observational studies in the medical literature[1–18] and stories in the news media and on the Internet allege that vaccines cause chronic diseases such as multiple sclerosis, diabetes, chronic arthritis, hay fever, and asthma. Because of these reports, some parents have chosen to delay or withhold vaccines for their children. In response to concerns by parents and health care professionals, the Institute of Medicine recently reviewed studies examining the relationship between multiple immunizations and immunologic dysfunction.[19]

We will discuss the pathogenesis of allergies, multiple sclerosis, type 1 diabetes, and chronic arthritis and the plausibility of biological mechanisms that explain how vaccines might cause these diseases. In addition, we will review well-controlled epidemiologic studies that investigate the relationship between vaccines and chronic diseases.

ALLERGIC DISEASES

Pathogenesis of Allergic Diseases

The pathogenesis of allergic diseases centers on the production of allergen-specific immunoglobulin E (IgE).

People with allergies have an exaggerated immune response characterized by increased production of allergen-specific IgE, binding of IgE to mast cells, and release by mast cells of specific mediators of inflammation (eg, histamine).[20] Inflammatory mediators induce a series of events causing contraction of smooth muscles, increased vascular permeability, hypersecretion of mucus, and consequent wheezing, urticaria, sneezing, rhinorrhea, or conjunctivitis.[20]

Several factors control production and release of IgE by B cells.[20] Inhaled allergens first come in contact with antigen-presenting cells that process allergens and present them to helper T cells. Helper T cells control B-cell secretion of IgE by releasing specific cytokines. Two types of helper T cells have been described. One type of helper T cell (T-helper cell type 2 or Th2) facilitates production of allergen-specific IgE and another (T-helper cell type 1 or Th1) decreases production of IgE.

Th1- and Th2-type responses are induced by different pathogens. Whereas Th2-type responses are induced by infections with worms and helminths, Th1-type responses are induced by infections with viruses and bacteria. Mechanisms proposed to explain how vaccines might cause allergic diseases focus on factors that prolong or enhance Th2-type (IgE-promoting) responses and decrease Th1-type (IgE-suppressive) responses.

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Mechanisms Proposed to Explain How Vaccines Might Cause Allergies

Understanding how vaccines might cause allergic diseases depends on understanding how Th1- and Th2-type responses develop. The fetus is not exposed typically to viruses or bacteria—infections that promote Th1-type responses. However, the fetus is exposed to common environmental allergens. Allergens are transferred transplacentally in maternal blood.[21] Transplacental exposure of the immune system to environmental allergens causes a skewing toward Th2-type responses at birth.[21] During the first few years of life, children encounter a variety of bacterial and viral infections that induce Th1-type responses and consequently promote a normal balance between Th1- and Th2-type responses.

One theory used to explain the increased incidence of allergic diseases in children is the "hygiene hypothesis," which states that better hygiene is associated with an increased risk of developing allergies.[22–28] Several epidemiologic findings support the hygiene hypothesis.[22–28] For example, children are less likely to have allergies if they are part of a large family, attend child care, experience a large number of infections early in childhood, or come in contact with animals. On the other hand, children are more likely to have allergies if they live in areas of better sanitation, are not infected with helminths or worms, or live a "Western" lifestyle.

The hygiene hypothesis proposes that a delay in early childhood infections prevents the development of Th1-type responses and allows for persistence of Th2-type responses initiated before birth. Because Th2-type responses promote secretion of IgE, the risk of allergic diseases is increased. Because vaccines prevent childhood infections, some investigators hypothesize that they might also prolong Th2-type responses and increase the risk of allergies.

However, the hypotheses that vaccines cause allergies by preventing childhood infections and that allergies are caused by Th1-Th2 imbalance are flawed for many reasons. First, vaccines do not prevent most common childhood infections. For example, a study of 25 000 illnesses in Cleveland in the 1960s found that children experienced 6 to 8 infections in the first 6 years of life; most of these infections were viral infections of the upper respiratory tract or intestine.[29] Viruses most likely to cause common childhood infections include rhinoviruses, influenza virus, parainfluenza virus, and rotavirus—diseases for which children are not immunized routinely. Indeed, the early childhood diseases that are associated with a decreased risk of allergies (and form the basis of the "hygiene hypothesis") are viral upper and lower respiratory tract infections.[22–28] Second, diseases prevented by vaccines, such as pertussis, measles, mumps, rubella, and varicella are highly contagious and easily transmitted independent of the degree of hygiene in the home or sanitation in the country. Third, children infected commonly with worms and helminths (infections that induce vigorous Th2-type responses) have a lesser incidence of allergies than do other children.[30] Similarly, conditions with strong Th2-responses such as idiopathic pulmonary fibrosis, pregnancy, or advanced melanoma are not associated with an increased incidence of allergies.[31] Fourth, diseases associated with strong Th1-type immune responses such as multiple sclerosis and type 1 diabetes occur in the same regions as those with an increased frequency of allergies.

Therefore, vaccines are unlikely to prevent most common childhood infections or to alter the normal balance of Th1- and Th2-type responses.

Clinical Studies Evaluating the Relationship Between Vaccines and Allergies

Several large epidemiologic studies have investigated the relationship between vaccines and allergies.[32–39] One well-controlled study was performed using the computerized records of children born between 1991 and 1997 who were enrolled in 4 large health maintenance organizations (HMOs).[32] This cohort was used to identify 18 407 children with asthma. Relative risks of asthma in vaccinated children were determined by comparison with children who did not receive vaccines. The relative risk for asthma was 0.92 for the combination diphtheria-tetanus-whole-cell pertussis vaccine, 1.09 for the oral polio vaccine, and 0.97 for the combination measles-mumps-rubella vaccine. In children who had at least 2 medical encounters during their first year of life, the relative risk for asthma was 1.07 after receipt of the *Haemophilus influenzae* type b (Hib) vaccine and 1.09 for the hepatitis B vaccine.

Another large well-controlled study prospectively evaluated the risk of allergies after receipt of the pertussis vaccine in 669 children.[33] Infants were randomized to receive 2-component diphtheria-tetanus-acellular pertussis vaccine; 5-component diphtheria-tetanus-acellular pertussis, diphtheria-tetanus-whole-cell pertussis; or diphtheria-tetanus (control group) beginning at 2 months of age. Children were followed for ~2.5 years and the risk of allergies was determined by parent questionnaires and examination of medical records. Allergic disorders studied included asthma, atopic dermatitis, allergic rhinoconjunctivitis, urticaria, and food allergies. No differences in the incidence of allergic diseases were observed in children who did or did not receive pertussis vaccine. Of interest, children with natural pertussis infections were more likely to develop allergic diseases than children not infected with pertussis.

Similarly, other controlled observational studies found no evidence that vaccines increased the risk for allergic diseases.[34–39]

Taken together, these studies fail to support the hypothesis that vaccines cause allergic diseases.

AUTOIMMUNE DISEASES

Pathogenesis of Autoimmune Diseases

The pathogenesis of autoimmune diseases is dependent on recognition of self-antigens by activated T or B cells.[40]

At least 4 conditions must be met for development of autoimmune disease.[40,41] First, self-reactive (autoreactive) T or B cells must be present. Although

many people have circulating autoreactive T and B cells, autoreactive cells typically are not pathogenic. This finding suggests that other factors are necessary for induction of autoimmunity. Second, self-antigens must be presented to the immune system in quantities sufficient to cause autoreactive cells to divide and mature. Third, additional signals such as cytokines are required to activate autoreactive T and B cells. Fourth, regulatory T cells must fail to control destructive autoimmune responses. Only when all of these conditions are met will expansion and activation of autoreactive lymphocytes and progression to autoimmune disease occur.

Mechanisms Proposed to Explain How Vaccines Might Cause Autoimmunity

Several infections cause autoimmune diseases. For example, *Borrelia burgdorferi* causes chronic arthritis[42] and group A β-hemolytic streptococcus causes rheumatic heart disease.[43] Theoretically, if infections can trigger autoimmune diseases, modified forms of infections (ie, immunizations) might also cause these diseases.

The mechanism by which natural infections are likely to cause autoimmune disease is termed "molecular mimicry." Because biological organisms share parts of many genes,[44] some microbial proteins are similar to human proteins. In responding to proteins found on invading microbes, the immune system might also respond inadvertently to self-proteins ("molecular mimicry") and cause damage.[45,46]

The relative capacity of natural infection or immunization to cause or exacerbate autoimmune diseases such as multiple sclerosis, type 1 diabetes, or chronic arthritis is discussed below.

MULTIPLE SCLEROSIS

Pathogenesis of Multiple Sclerosis

The pathologic hallmark of multiple sclerosis is the loss of myelin in the central nervous system.[47] Axonal demyelination causes slowing or loss of nerve conduction and results in symptoms of multiple sclerosis.[47]

Although multiple sclerosis is clearly an immune-mediated disorder in genetically susceptible individuals, the sequence of events that initiates the disease is unknown.[47] Activated self-reactive T cells are believed to infiltrate the central nervous system, attach to self-antigens (eg, myelin basic protein [MBP]), and cause demyelination.[48]

Mechanisms Proposed to Explain How Vaccines Might Cause Multiple Sclerosis

Both hepatitis B and influenza vaccines have been proposed to cause or exacerbate multiple sclerosis by the process of molecular mimicry.

The concept that molecular mimicry might cause autoimmune disease in the central nervous system was first tested in 1985.[49] Rabbits were inoculated with a peptide contained within the hepatitis B virus polymerase protein that was identical to a region of rabbit MBP. Peptide was administered in a potent adjuvant consisting of a mixture of mineral oil and killed mycobacterial bacilli. Four of 11 rabbits inoculated with this shared peptide developed experimental autoimmune encephalomyelitis. This finding launched the notion that immunization with hepatitis B vaccine might cause multiple sclerosis. The hypothesis was further fueled by anecdotal reports of multiple sclerosis after hepatitis B immunization[50,51] and 2 case-control studies showing a small increase in the incidence of multiple sclerosis in vaccinated individuals that was not statistically significant.[52–54] As a consequence of these reports, the French government temporarily suspended their school-based program of hepatitis B vaccination.

However, the hypothesis that hepatitis B vaccine causes multiple sclerosis is flawed for several reasons. First, the only protein contained in the hepatitis B vaccine, hepatitis B surface antigen (HBsAg), is not similar to human MBP.[55] Therefore, studies of hepatitis B virus polymerase protein in rabbits are irrelevant to studies of hepatitis B vaccine in humans. Second, natural infection with hepatitis B virus is associated with production of large quantities of HBsAg, but is not associated with an increased risk of developing multiple sclerosis. During natural infection with hepatitis B virus, concentrations of HBsAg particles often exceed 100 μg/mL and may exceed 500 μg/mL. An adult with an average blood volume of 4000 mL will have at least 400 000 μg of HBsAg in the circulation after natural infection.[56] In contrast, the hepatitis B vaccine contains only 10 to 40 μg of HBsAg. Therefore, the quantity of HBsAg found in the blood of an infected adult is ~10 000-fold greater after natural infection than immunization. Consistent with the fact that hepatitis B virus infections are not associated with an increased risk of developing multiple sclerosis, regions associated with high rates of infection with hepatitis B virus (eg, Asia) are distinct from those associated with high rates of multiple sclerosis (eg, North America).

On the other hand, influenza vaccine appears to be a plausible candidate for molecular mimicry in the central nervous system. Influenza virus type A contains a protein that is similar to human MBP,[57] and natural infection with influenza virus exacerbates symptoms in patients with multiple sclerosis.[58]

Clinical Studies Evaluating the Relationship Between Vaccines and Multiple Sclerosis

The capacity of vaccines (including hepatitis B and influenza) to either cause or exacerbate multiple sclerosis has been evaluated in several well-controlled epidemiologic studies.[58–62]

Two large case-control studies evaluated whether the hepatitis B vaccine causes multiple sclerosis[59] or whether hepatitis B, tetanus, or influenza vaccines exacerbate symptoms of multiple sclerosis.[60] The first study used a cohort of 121 700 nurses followed from 1976 and 116 671 nurses followed from 1989 to identify 192 women with multiple sclerosis and 645 matched controls.[59] Vaccination status was determined by mailed questionnaires and confirmed by means of vaccination certificates. The multivariate relative risk of multiple sclerosis associated with exposure to the hepatitis B vaccine was 0.9, and the

relative risk within 2 years before the onset of disease was 0.7. There was no association between the number of doses of hepatitis B vaccine and the risk of multiple sclerosis. The second study included 643 patients with a relapse of symptoms of multiple sclerosis occurring between 1993 and 1997 identified from the European Database for Multiple Sclerosis.[60] Relapse was defined as a relapse of symptoms after a symptom-free period of at least 12 months and confirmed by a visit to a neurologist. Vaccination status was determined initially by telephone interviews and confirmed by means of medical records. Exposure to vaccination in the 2-month period before relapse was compared with the 4 previous 2-month control periods to determine relative risks. The relative risk of relapse associated with the use of any vaccine was 0.71 and with the hepatitis B, tetanus, and influenza vaccines was 0.67, 0.75, and 1.08, respectively. Therefore, vaccines do not appear to either cause or exacerbate symptoms of multiple sclerosis.

Additional well-controlled studies also found that influenza vaccine did not exacerbate symptoms of multiple sclerosis.[57,61,62] Indeed, in a retrospective study of 180 patients with relapsing multiple sclerosis, infection with influenza virus was more likely than immunization with influenza vaccine to cause an exacerbation of symptoms.[57] Consistent with this observation, MBP-specific T cells were mildly stimulated after natural influenza infection but not after influenza immunization.[57] Because wild-type influenza virus is well-adapted to growth in respiratory epithelia, and because influenza vaccine does not contain replicating virus, natural infection is more likely than vaccination to produce quantities of self-antigens and induce concentrations of cytokines necessary to trigger MBP-specific T cells. Taken together, these findings suggest that influenza vaccine is more likely to prevent than cause exacerbations of multiple sclerosis.

TYPE 1 DIABETES MELLITUS

Pathogenesis of Diabetes Mellitus

Type 1 diabetes is attributable to a deficiency of insulin caused by destruction of pancreatic islet cells.[63] Antibodies directed against pancreatic islet-cell proteins (ie, autoantibodies) are present in the blood of patients with type 1 diabetes.[64–68] About 90% of patients recently diagnosed with type 1 diabetes will have antibodies to 1 or more of these islet-cell proteins.[69] In contrast, islet-cell autoantibodies are found in only 1% of healthy controls.[69]

Mechanisms Proposed to Explain How Vaccines Might Cause Type 1 Diabetes

Natural infections are likely to cause type 1 diabetes in genetically susceptible individuals. Therefore, some investigators have hypothesized that modified forms of infection, like immunization, might also cause type 1 diabetes.

The likelihood that natural viral infections cause type 1 diabetes is supported by several observations. First, ~20% of children infected with natural rubella virus in utero develop type 1 diabetes.[70] Second, children infected with natural rubella virus postnatally have higher levels of islet-cell autoantibodies than do rubella-seronegative children.[71] Third, maternal enterovirus-specific antibodies are greater in children with type 1 diabetes than in those without disease, suggesting that in utero infection with enteroviruses might in part cause type 1 diabetes.[72] Fourth, coxsackie virus B4 was detected in the pancreas of a child who died soon after developing diabetic ketoacidosis.[73] Coxsackie B4 virus contains a protein similar to a pancreatic islet-cell protein. Therefore, molecular mimicry after natural enterovirus infection might induce destructive islet-cell autoantibodies.[72] However, definitive mechanisms by which viral infections cause autoimmune diabetes have not been firmly established.[74]

Clinical Studies Evaluating the Relationship Between Vaccines and Type 1 Diabetes

The hypothesis that the timing of vaccines either causes or prevents type 1 diabetes was first tested in uncontrolled observational studies. Investigators found a lower incidence of type 1 diabetes in populations using bacille Calmette-Guerin vaccine at birth.[75] Similarly, 1 study in Finland found a higher incidence of type 1 diabetes in children who received 4 doses of Hib vaccine at 3, 4, 6, and 14 months of age than in those who received 1 dose of Hib vaccine at 14 months of age.[75] Media coverage of these studies might have caused some parents to delay immunizations for their children. However, subsequent studies found that early administration of bacille Calmette-Guerin vaccine did not prevent type 1 diabetes.[76,77] Also, the analytical methods used in the Finnish study of Hib vaccine were incorrect, and there were no significant differences in the incidence of type 1 diabetes in Hib-vaccinated infants 10 years later.[78] In addition, 21 421 children who received the Hib conjugate vaccine between 1988 and 1990 in the United States were followed for 10 years and the risk of type 1 diabetes was 0.78 when compared with a group of 22 557 children who did not receive the vaccine.[79]

Another well-controlled study evaluating the relationship between vaccines and type 1 diabetes was that performed using data from the Vaccine Safety DataLink.[80] Four large HMOs were used to identify children with type 1 diabetes born between 1988 and 1997. All 4 HMOs maintained registries of children with diabetes and cases were confirmed by means of medical records. Two hundred fifty-two cases of type 1 diabetes were compared with 768 matched controls. The odds ratio was 0.28 for the association between diabetes and the whole-cell pertussis vaccine, 1.36 for the measles-mumps-rubella vaccine, 1.14 for the Hib vaccine, 0.81 for the hepatitis B vaccine, 1.16 for the varicella vaccine, and 0.92 for the acellular-pertussis vaccine. For children vaccinated at birth with the hepatitis B vaccine the odds ratio for diabetes was 0.51 and for those vaccinated at 2 months of age or later was 0.86. In accord with the Vaccine Safety DataLink study, several other well-controlled retrospective studies found that immuni-

zations were not associated with an increased risk of developing type 1 diabetes.[81–83]

Therefore, the best available evidence does not support the hypothesis that vaccines cause type 1 diabetes.

CHRONIC ARTHRITIS

Pathogenesis of Chronic Arthritis in Lyme Disease

One of the most intriguing hypotheses to explain how an infection could cause an autoimmune disease is that used to explain the pathogenesis of chronic Lyme arthritis.

Lyme disease is caused by the bacterium, *Borrelia burgdorferi*. Approximately 60% of untreated adults with Lyme disease will develop acute arthritis, and ~10% of these patients will develop chronic arthritis that is resistant to treatment with antibiotics.[84] Chronic treatment-resistant arthritis is characterized by the presence of T cells within the affected joint directed against 1 outer surface protein of the bacteria (outer surface protein A [OspA]).[85] Additional evidence for the fact that chronic Lyme arthritis is immunologically mediated is that it occurs primarily in patients with 1 particular HLA haplotype (HLA-DR4)[86] and that *B burgdorferi* DNA is absent from the synovial fluid of affected patients.[87]

Mechanisms Proposed for How Lyme Vaccine Might Cause Chronic Arthritis

The mechanism proposed to explain how natural infection with *B burgdorferii* (or immunization with Lyme vaccine) might cause chronic arthritis is molecular mimicry. Symptoms of chronic arthritis in Lyme disease patients are mediated by a T-cell response directed against OspA,[88] and the Lyme vaccine (LYMErix; GlaxoSmithKline, Philadelphia, PA) consists of OspA only. OspA is similar to a protein contained on human lymphocytes called lymphocyte function-associated antigen-1 (LFA-1).[88] The following sequence of events is proposed to explain how natural Lyme infection could cause chronic, immune-mediated arthritis.[84] After *B burgdoferi* invades the joints, bacteria are processed by antigen-presenting cells, and OspA-specific T cells are recruited into the synovial fluid. OspA-specific T cells secrete cytokines that increase the expression of LFA-1 on T cells. As T cells in the joint die, they are phagocytosed by macrophages, and LFA-1 is processed and presented to the immune system. Chronic arthritis occurs in the absence of bacteria when OspA-specific T cells within the joint are continually stimulated by LFA-1.

When the Lyme vaccine was licensed by the Food and Drug Administration in December 1998, sequence similarities between OspA and LFA-1 and the hypothesis that LFA-1-specific T cells might be responsible for chronic arthritis were known. Because the Lyme vaccine had the theoretical potential to cause chronic arthritis, the Centers for Disease Control and Prevention advised that the Lyme vaccine "should be considered for use" in people at risk.[89] The Centers for Disease Control and Prevention did not fully "recommend" the vaccine for persons at risk in part because it was unclear whether the Lyme vaccine would be a rare cause of chronic arthritis.

Clinical Studies Evaluating the Relationship Between Lyme Vaccine and Chronic Arthritis

Two large, prospective, placebo-controlled studies were performed evaluating the safety of Lyme vaccine.[90,91] Lyme vaccines containing OspA linked to aluminum hydroxide[90] or without adjuvant[91] were compared with placebo in 10 936 and 10 305 subjects, respectively. Participants were followed for 20 to 24 months. There were no significant differences in the type or frequency of joint symptoms in vaccine and placebo recipients in either study. Similarly, patients with a previous history of Lyme disease did not experience an increased frequency of joint symptoms compared with controls.

Between December 1998 and August 2000, ~1.5 million doses of the Lyme vaccine were distributed in the United States.[92] Unexpected or unusual patterns of reporting of chronic arthritis to the Vaccine Adverse Event Reporting System, including in people with a past history of Lyme disease or HLA-DR4 haplotype, did not occur.[92] However, because Vaccine Adverse Event Reporting System is a passive reporting system and does not include comparisons between vaccinated and unvaccinated individuals, interpretations about vaccine safety are limited.

The finding that Lyme disease, but not Lyme vaccine, induces chronic arthritis is consistent with important differences between natural infection and immunization. Natural infection with *B burgdorferii* may result in bacterial replication and inflammation in joints causing a high bacterial antigenic load and release of large quantities of cytokines into synovial fluid. However, because the Lyme vaccine does not contain replicating bacteria, none of these events occur after immunization. Ironically, the best way to prevent chronic Lyme arthritis in genetically susceptible individuals might be by vaccination. Unfortunately, because the Lyme vaccine is no longer available, testing this hypothesis will be difficult.

CONCLUSION

Several mechanisms have been proposed to explain how vaccines might cause allergic or autoimmune diseases. However, flaws in proposed mechanisms are consistent with large well-controlled epidemiologic studies that do not support the hypothesis that vaccines cause chronic diseases. Furthermore, because infections with wild-type bacteria or viruses are more likely to expose self-antigens and induce levels of cytokines greater than that found after immunization with attenuated or avirulent pathogens, some vaccines are probably more likely to prevent or modify than cause or exacerbate autoimmune diseases (eg, Lyme vaccine for genetically susceptible individuals, or influenza vaccine for patients with multiple sclerosis).

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"The older I grow the more I distrust the familiar doctrine that age brings wisdom."

—H. L. Mencken

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